TARGET

STUDIES EMULATING A TARGET TRIAL

Transparent reporting of studies emulating a target trial: the TARGET guideline

James McAuley

CENTRE FOR PAIN IMPACT

Neuroscience Research Australia
Discover — Conquer — Cure

UNSW SYDNEY
Medicine & Health

Disclosures

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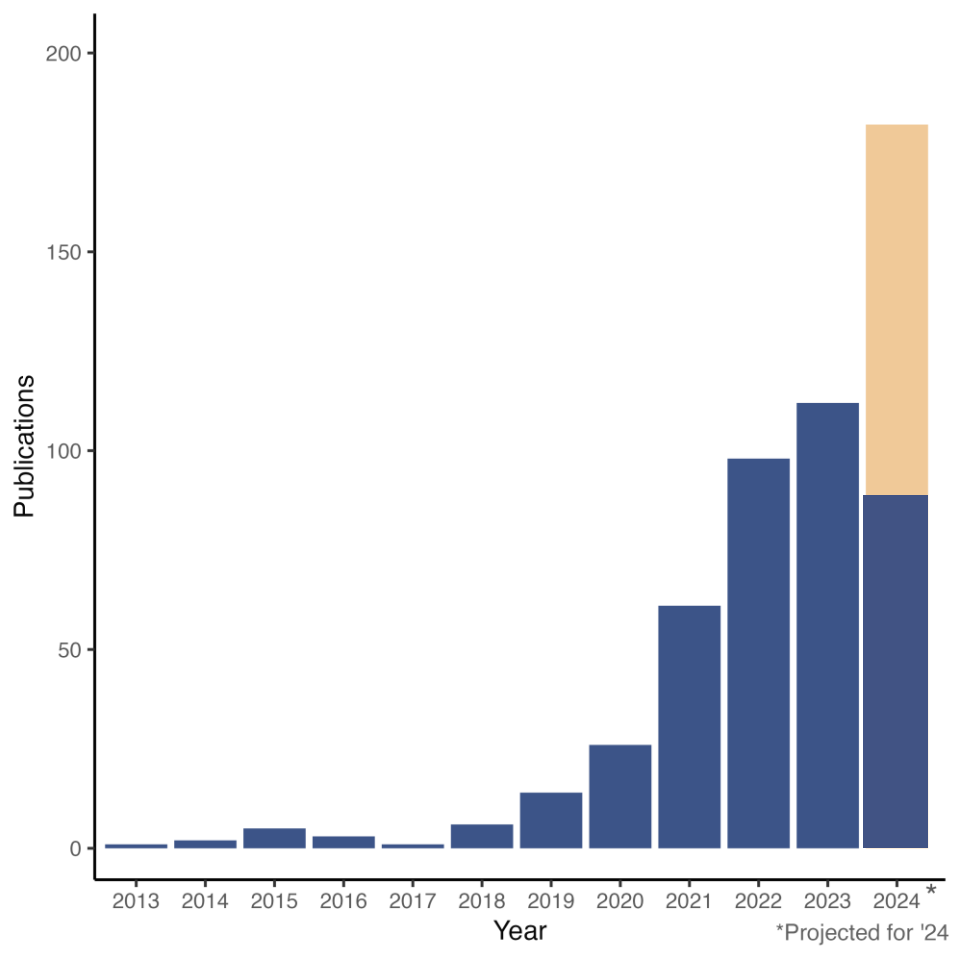
Increasing use of target trial framework

- Published studies increasing annually
- Journals (JAMA, Annals of Internal Medicine, Epidemiology) identify the framework as useful
- Regulators (FDA, EMA, NICE, TGA) reviewing use of observational data to inform policy decision-making



JAMA Network | Open

Original Investigation | Statistics and Research Methods

Reporting of Observational Studies Explicitly Aiming to Emulate Randomized Trials
A Systematic Review

Harrison J. Hansford, BSc(Hons); Aidan G. Cashin, PhD; Matthew D. Jones, PhD; Sonja A. Swanson, ScD; Nazrul Islam, MD, PhD; Susan R. G. Douglas, BExPhys; Rodrigo R. N. Rizzo, PhD; Jack J. Devonshire, BSc(Hons); Sam A. Williams, BSc(Hons); Issa J. Dahabreh, MD, ScD; Barbra A. Dickerman, PhD; Matthias Egger, MD, MSc; Xabier Garcia-Albeniz, MD, PhD; Robert M. Golub, MD; Sara Lodi, PhD; Margarita Moreno-Betancur, PhD; Sallie-Anne Pearson, PhD; Sebastian Schneeweiss, MD, ScD; Jonathan A. C. Sterne, PhD; Melissa K. Sharp, PhD; Elizabeth A. Stuart, PhD; Miguel A. Hernán, MD, DrPh; Hopin Lee, PhD; James H. McAuley, PhD

Aims

To describe how studies that explicitly aimed to emulate a target trial are reported

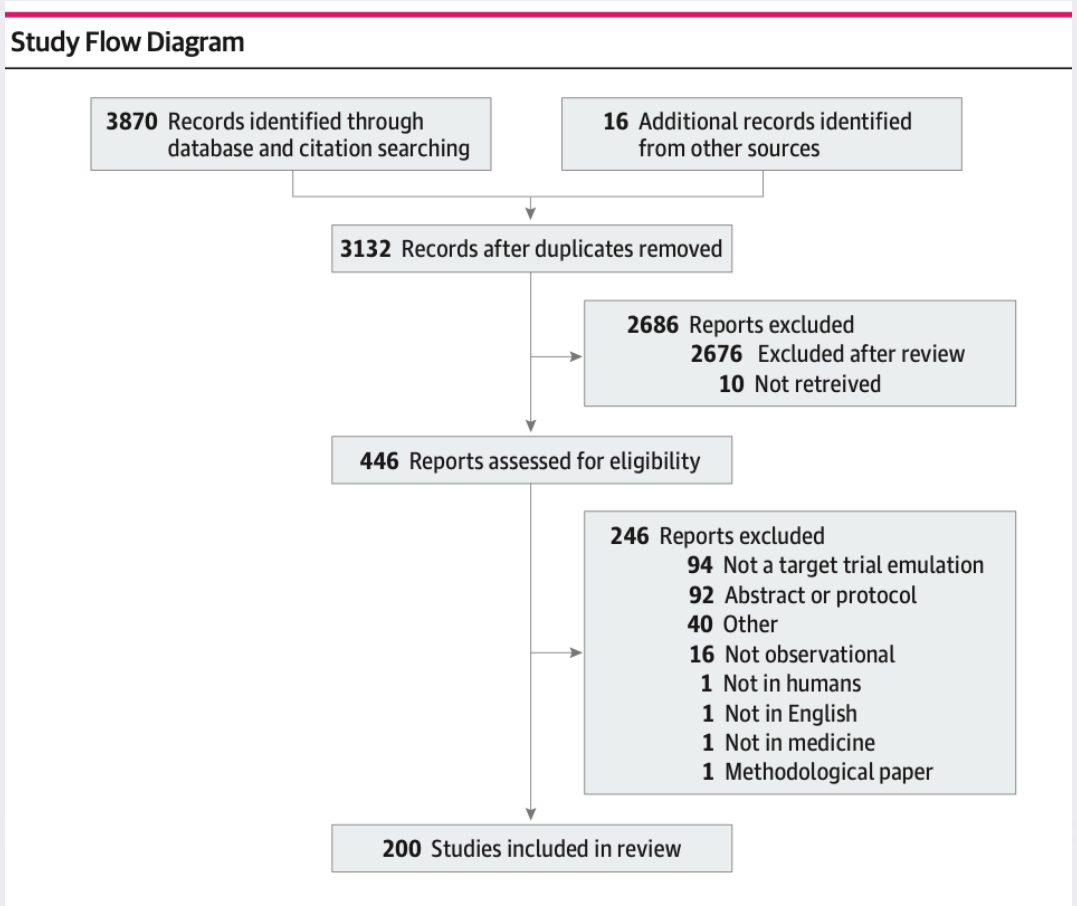
To determine which reporting guidelines are used

Included studies

Published cohort or case control studies that explicitly stated an attempt to emulate a target trial

Results

- 200 studies included (up to 2023)
- Infectious diseases (43), cardiology (30) and oncology (30)
- 80% used electronic health records or claims data
- Median sample size was ~11,000 individuals
- Most compared pharmacological treatment strategies
- Common outcomes were death (72), cardiovascular events (19), cancer (8)



Reporting of the target trial protocol

Protocol component	%
Eligibility criteria	97
Interventions	95
Treatment assignment	91
Outcomes	98
Follow up period	98
Causal contrast	73
Data analysis plan	97
Clearly defined time-zero	82

58% reported all protocol components of the target trial

Reporting of the target trial emulation

- 74% identified target trial emulation in the abstract
- 96% stated the type of treatment strategy investigated
  - dose (19%)
  - duration (13%)
  - frequency (12%)
- 22% cited a reporting guideline; 67% used STROBE

Reporting of target trial emulations is sub-optimal

- time-zero, treatment strategies, causal contrast

More guidance for authors reporting a target trial emulation is needed

Open access Protocol

BMJ Open

Development of the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline

Harrison J Hansford [1,2] Aidan G Cashin [1,2] Matthew D Jones,[1,2] Sonja A Swanson,[3,4,5] Nazrul Islam,[6,7] Issa J Dahabreh,[4,5,8] Barbra A Dickerman,[4,5] Matthias Egger [9,10,11] Xavier Garcia-Albeniz,[4,12] Robert M Golub,[13] Sara Lodi,[4,14] Margarita Moreno-Betancur,[15,16] Sallie-Anne Pearson,[17] Sebastian Schneeweiss,[18] Jonathan Sterne [19,20,21] Melissa K Sharp,[22] Elizabeth A Stuart,[23] Miguel A Hernan,[4,5,8] Hopin Lee,[24,25] James H McAuley[1,2]

Aim

To develop a reporting guideline of analyses of observational data that aim to estimate causal effects by explicitly emulating a target trial

Scope

Emulation of a parallel group, individually randomized target trial, with adjustment for baseline confounders in an attempt to emulate randomized assignment

Stage 1: Identify Current Reporting Practices

- Establish working group
- Systematic review of the literature to examine the items reported in published studies explicitly using the target trial framework

Dr Aidan Cashin

Mr Harrison Hansford

Prof Miguel Hernán

Dr Hopin Lee

Dr Matthew Jones

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A/Prof Sonja Swanson

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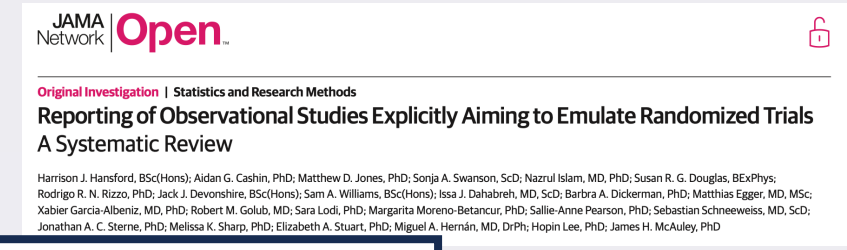

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Enhancing the QUAlity and Transparency Of health Research

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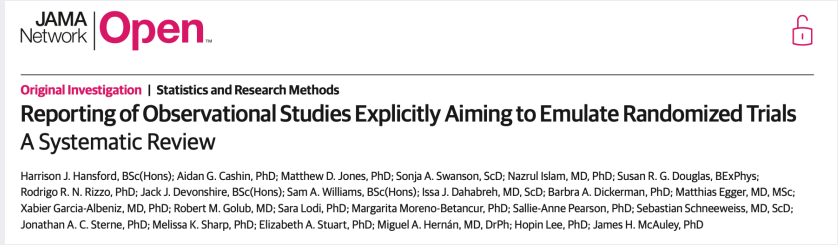

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Stage 2: Identify and Refine Items

- Generate reporting items based upon themes in existing literature related to target trial emulation
- Online surveys to identify and refine potential reporting items to be considered at the consensus meeting

Survey

Aim: to identify and refine items proposed based on the systematic review and published guidance

Participants: experts in methodology, epidemiology, clinical trials, biostatistics, reporting guideline development and journal editors

Results: Identified 4 new items, removed 2 items and refined 33 items

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Stage 3: Prioritise and Consolidate Items

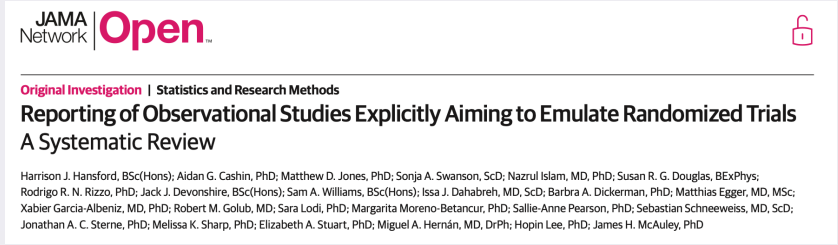
- Consensus meeting to consolidate and prioritise key items to be included in the TARGET guideline and to structure an explanation and elaboration document

Consensus meeting

3 days – attended by 90% of the team

Refined 32 items, added 2 items, removed 4 items

Agreed on 40 items to be included in guideline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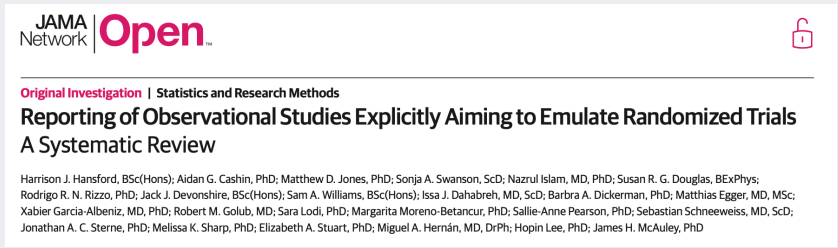
Stage 4: Write up and Pilot Draft Guidance

- Write up of draft TARGET guideline and accompanying explanation and elaboration document
- Pilot the draft documents with potential users of the guideline

Stage 5: Guideline Implementation

- Publication of TARGET guideline and explanation and elaboration document
- Dissemination of TARGET guideline to stakeholders including resources to support implementation



Survey

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Enhancing the QUAlity and Transparency Of health Research

TARGET guideline

TARGET
STUDIES EMULATING A TARGET TRIAL

Item no.		Checklist item		
Abstract				
1	a	Identify that the study attempts to emulate a target trial using observational data. State the objectives and briefly summarize the specified target trial.		
	b	Report the observational data source used for emulation.		
	c	Summarise statistical methods, key assumptions, findings and conclusions.		
Introduction				
2	Background & rationale			
	a	Describe the scientific background of the study and the gap in knowledge.		
	b	State the causal question.		
	c	Describe the rationale for using the target trial framework with the available data. Cite randomized trials informing t the target trial if applicable.		
Methods				
3	Data source(s)	Cite the data source(s) contributing to the analyses and for each one describe the following: original purpose, type, the geographic location(s), setting and time-period. If relevant, describe how the data were linked or pooled.		
	Target trial specification Specify the components of the protocol of the target trial that would answer the causal question.		**Target trial emulation** Describe how the components of the protocol of the target trial were emulated with the observational data, including how all variables were measured or ascertained.	
4	**Eligibility Criteria**			
	a	Describe the eligibility criteria.	b	Describe how the eligibility criteria were operationalized with the data.
5	**Treatment strategies**			
	a	Describe the treatment strategies that would be compared.	b	Describe how the treatment strategies were operationalized with the data.
6	**Assignment Procedures**			
	a	Identify that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.	b	Describe how assignment to treatment strategies was operationalized with the data.
7	**Follow-up**			
	a	Clarify that follow-up would start at assignment to the treatment strategies. Specify when follow-up would end.	b	Clarify that follow-up would start at assignment to the treatment strategies. Describe how the end of follow-up was operationalized with the data.
8	**Outcome(s)**			
	a	Describe the outcome(s).	b	Describe how the outcome(s) were operationalized with the data.
9	**Causal contrast(s)**			
	a	Describe the causal contrast(s) of interest (e.g., intention to treat effect, per-protocol effect), including effect measure(s).	b	Describe the observational analogues of the causal contrast(s), including effect measure(s).

Introduction

Background and Rationale

Describe the study background and theoretical rationale for investigating the mechanisms of interest. Include supporting evidence or the theoretical rationale for why the intervention or exposure might affect the proposed mediators and why the mediators might affect the outcomes.

Explanation | A concise description of the study background should be included to provide context for the subject matter and clinical setting of the study. Most often, mediation analyses will be used to understand the mechanisms by which an intervention or exposure might affect an outcome. It is recommended that authors make clear why mediation analyses helps to answer the substantive scientific question. Describing the theory that underpins the proposed mechanisms of interest, stating why the exposure or intervention is expected to affect the proposed mediator (action theory), and why the mediator is expected to affect the outcome (conceptual theory) is recommended.[12] This type of rationale should reflect each objective and, when possible, should be supported with empirical or qualitative evidence.

from AGReMA Statement, *JAMA* 2021

Piloting TARGET

Student/postdocs

- Refined 30 items

Stakeholders identified through stakeholder mapping

- Epidemiologists, clinical researchers, clinicians
- Regulators
- Journal editorial staff
- Industry

Link to sign up to pilot the guideline

TARGET outcomes

Submit TARGET for publication in early 2025

Website with materials to assist reporting

- Editable checklist
- Participant flow diagrams
- Target trial protocol table(s)

Explanation and elaboration document mid 2025

Impact evaluation 2026-7

Link to sign up to pilot the guideline

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Dr Melissa Sharp
Prof Elizabeth Stuart
Prof Sonja Swanson

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TARGET pilot

Link to sign up to pilot the guideline

Methods

	Target trial specification (Items 4-6)	Specify the components of the protocol of the target trial that would answer the causal question.		Target trial emulation (Items 7-9)	Describe how the components of the protocol of the target trial were emulated with the observational data, including how all variables were measured or ascertained.
4	Definition of causal estimand(s)		**7**	Operationalization of causal estimand(s)	
	a	**Eligibility criteria:** Describe the eligibility criteria.		a	**Eligibility criteria**: Describe how the eligibility criteria were operationalized with the data.
	b	**Treatment strategies:** Describe the treatment strategies that would be compared.		b	**Treatment strategies**: Describe how the treatment strategies were operationalized with the data.
	c	**Assignment procedures:** Clarify that eligible individuals would be randomly assigned to treatment strategies and may be aware of their treatment allocation.		c	**Assignment procedures**: Describe how assignment to treatment strategies was operationalized with the data.
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	e	**Outcome(s):** Describe the outcome(s).		e	**Outcome(s)**: Describe how the outcome(s) were operationalized with the data.
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Summary

Observational studies are increasingly using the target trial framework however reporting is heterogenous

TARGET guideline developed to improve reporting by:

- Establishing an expert working group
- Review of current application of the framework
- Identify and refine items
- Consensus on items to be included in the guideline
- Piloting the guideline with stakeholders

Aim to publish the checklist and explanation and elaboration documents provide resources to support uptake

Link to sign up to pilot the guideline

Further evidence on reporting quality

Papers	Journal (DOI)	Number of studies	Conclusions
Hansford 2023	JAMA Network Open (10.1001/jamanetworkopen.2023.36023)	200	"**Reporting of how the target trial was emulated was inconsistent.** A reporting guideline for studies explicitly aiming to emulate a target trial may improve the reporting of the target trial protocols and other aspects of these emulation attempts"
Zuo 2023	Journal of Clinical Epidemiology (10.1016/j.jclinepi.2023.08.003)	96	"**Uneven adherence to the TTE framework exists**, and future improvements are needed to progress applications using causal inference with observational data"
Smit 2023	NPJ Digital Medicine (10.1038/s41746-023-00961-1)	79	"To achieve actionable AI in the ICU, we advocate **careful consideration of the causal question of interest**, describing this research question as a target trial emulation, usage of appropriate causal inference methods, and **acknowledgement (and examination of potential violations of) the causal assumptions**."
Scuola 2023	BMC Medical Research Methodology (10.1186/s12874-023-02000-9)	38	Different methods can be leveraged to address (A) confounding bias, (B) immortal time bias, and (C) selection bias. **When working with observational data, and if possible, the 'target trial' framework should be used as it provides a structured conceptual approach to observational research**.
Bigirumurame 2022	BMJ Open (10.1136/bmjopen-2022-070963)	NA	Protocol for review
Leal 2022	Frontiers in Pharmacology (10.3389/fphar.2022.904824)	NA	Protocol for review

Methods cont.

5	Identifying assumptions	Describe assumptions that would be made to identify each causal estimand. Describe the variables, if any, related to these assumptions.	**8**	Identifying assumptions	Describe assumptions made to estimate each causal estimand, including assumptions regarding baseline confounding due to lack of randomisation. Describe the variables related to these assumptions and how they were operationalized with the data.
6	Data analysis plan	For each causal estimand, describe the data analysis plan and its modelling assumptions.	**9**	Data analysis plan	
				a	For each causal estimand, describe the data analysis plan and its modelling assumptions.
				b	For each causal estimand, describe any additional analyses conducted to assess the robustness of the results to potential violations of assumptions and choices about the design and analysis.
10	Ethics	If relevant, provide the institutional research board or ethics committee that approved the study and approval number(s).			

M

Abstract

Introduction

Methods

Results

Discussion

Open Science

PPI

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Methods		
3	Data source(s)	Cite the data source(s) contributing to the analyses and for each one describe the following: original purpose, type, the geographic location(s), setting and time-period. If relevant, describe how the data were linked or pooled.
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11	**Data analysis plan**	
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		b.ii. For each causal estimand, describe any additional analyses conducted to assess the robustness of the results to potential violations of assumptions and choices about the design and analysis.
12	Ethics	If relevant, provide the institutional research board or ethics committee that approved the study and approval number(s).
Results		
13	Participant selection	
	a	Report numbers of individuals assessed for eligibility, eligible individuals and individuals excluded with reasons.
	b	Report numbers of individuals in each treatment strategy at baseline and at relevant times during the follow up. If applicable, explain if individuals entered the analysis multiple times.
	c	Using a flow chart is strongly recommended.
14	Baseline data	Present information on relevant characteristics of individuals at baseline, by treatment strategy.
15	Follow-up	For each analysis and treatment strategy, summarize length of follow-up and describe reasons for end of follow-up.
16	Missing data	Describe the frequency of missing data in all variables, by treatment strategy, when applicable.
17	Outcomes	Report descriptive statistics for each outcome, by treatment strategy.
18	Estimates	Report the estimates for all analyses with corresponding measures of precision, including both absolute and relative measures of effect, when applicable.
19	Additional analyses	Report results of all analyses to assess the robustness of the findings to potential violations of assumptions and choices about the design and analysis.
Discussion		
20	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomization.
21	Interpretation	Provide an interpretation of the key findings given the limitations, precision of estimates and existing literature.
Open science		
22	Registration	State whether, when and where the study protocol was registered.
23	Sharing of study materials	Provide information on whether data, analytic code and/or other materials are accessible, and where and how they can be accessed.
24	Funding source(s)	Provide the source(s) of funding and detail the role of the funder(s) in the design, conduct and reporting of the study.
25	Conflicts of interest	State any conflicts of interest and financial disclosures for all authors.
Patient and public involvement		
26		Describe if and how patients and the public were involved in the design, conduct and/or reporting of the study.

Current Checklist

Item No.	Section	Checklist item
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	b	Summarize the specified target trial, observational data used for emulation, statistical methods, key assumptions, findings and conclusions.
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2	Background & Rationale	
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Methods		
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13	Participant selection			
	a	Report numbers of individuals assessed for eligibility, eligible individuals and individuals excluded with reasons.		
	b	Report numbers of individuals in each treatment strategy at baseline and at relevant times during the follow up. If applicable, explain if individuals entered the analysis multiple times.		
	c	Using a flow chart is strongly recommended.		
14	Baseline data	Present information on relevant characteristics of individuals at baseline, by treatment strategy.		
15	Follow-up	For each analysis and treatment strategy, summarize length of follow-up and describe reasons for end of follow-up.		
16	Missing data	Describe the frequency of missing data in all variables, by treatment strategy, when applicable.		
17	Outcomes	Report descriptive statistics for each outcome, by treatment strategy.		
18	Estimates	Report the estimates for all analyses with corresponding measures of precision, including both absolute and relative measures of effect, when applicable.		
19	Additional analyses	Report results of all analyses to assess the robustness of the findings to potential violations of assumptions and choices about the design and analysis.		
Discussion				
20	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomization.		
21	Interpretation	Provide an interpretation of the key findings given the limitations, precision of estimates and existing literature.		
Open science				
22	Registration	State whether, when and where the study protocol was registered.		
23	Sharing of study materials	Provide information on whether data, analytic code and/or other materials are accessible, and where and how they can be accessed.		
24	Funding source(s)	Provide the source(s) of funding and detail the role of the funder(s) in the design, conduct and reporting of the study.		
25	Conflicts of interest	State any conflicts of interest and financial disclosures for all authors.		
Patient and public involvement				
26		Describe if and how patients and the public were involved in the design, conduct and/or reporting of the study.		

Discussion + other

Discussion		
18	Limitations	Discuss the limitations of the study considering differences between the target trial and its emulation and the plausibility of assumptions, including assumptions regarding baseline confounding due to lack of randomisation.
19	Interpretation	Provide an interpretation of the key findings given the limitations, precision of estimates and existing literature.
Open science		
20	Registration	State whether, when and where the study protocol was registered.
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Patient and public involvement		
25		Describe if and how patients and the public were involved in the design, conduct and/or reporting of the study.

10	**Identifying assumptions**			
		Describe assumptions that would be made to identify each causal estimand. Describe the variables, if any, related to these assumptions.		Describe assumptions made to estimate each causal estimand, including assumptions regarding baseline confounding due to lack of randomization. Describe the variables related to these assumptions and how they were operationalized with the data.
11	**Data analysis plan**			
	a	For each causal estimand, describe the data analysis plan and its modelling assumptions.	b.i.	For each causal estimand, describe the data analysis plan and its modelling assumptions.
			b.ii.	For each causal estimand, describe any additional analyses conducted to assess the robustness of the results to potential violations of assumptions and choices about the design and analysis.
12	Ethics	If relevant, provide the institutional research board or ethics committee that approved the study and approval number(s).		
Results				
13	Participant selection			
	a	Report numbers of individuals assessed for eligibility, eligible individuals and individuals excluded with reasons.		
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